Docket No.: 31126/41458UTL
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Ledbetter *et al.*

Application No.: 10/053,530 Confirmation No.: 8993

Filed: January 17, 2002 Art Unit: 1642

For: Binding Domain Immunoglobulin Fusion Proteins Examiner: Blanchard, David

DECLARATION OF ALAN F. WAHL

1. I, Alan F. Wahl, declare as follows.

2. I am the Vice President, Technology Research, at Trubion Pharmaceuticals, Inc., the assignee of the above-identified patent application. A copy of my Curriculum Vitae is attached hereto as Exhibit 1.

3. Various single chain proteins were made that include a binding domain capable of binding a target biological molecule joined to a IgG hinge peptide with two cysteine residues (one at the cysteine position responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG antibody) further joined to immunoglobulin heavy chain CH2 and CH3 constant region polypeptides. A number of the single chain proteins were demonstrated to promote antibody-dependent, cell-mediated cytotoxicity (ADCC) and/or complement fixation.

4. Examples of such single chain proteins that were made are:

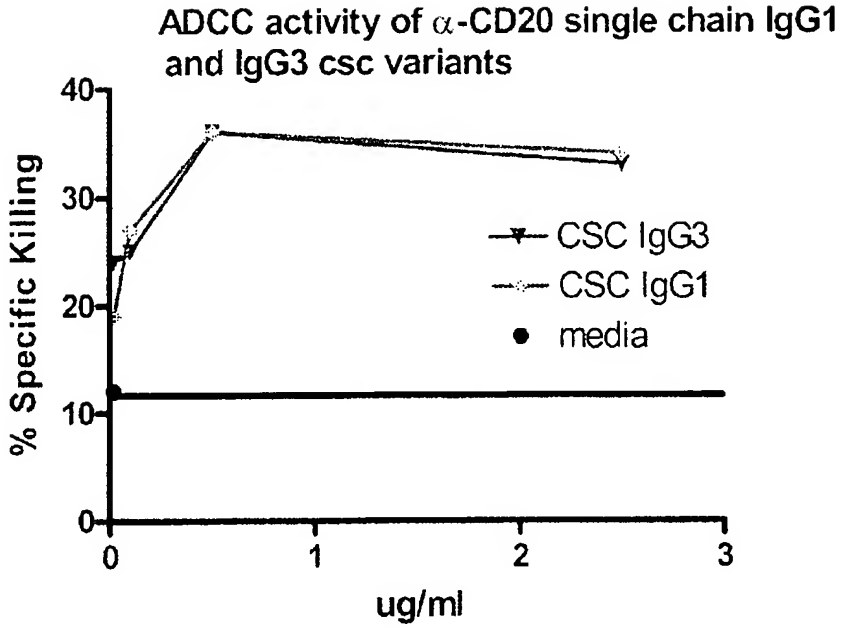
Single chain protein	Binding domain target	Hinge	CH2	CH3
1 (TRU-015)	CD20	IgG_1 CSC	IgG_1	IgG_1
2	CD20	IgG_1 CCS	IgG_1	IgG_1
3	CD37	IgG_1 CSC	IgG_1	IgG_1
4	CD20	IgG_3 CSC	IgG_1	IgG_1

5. Single chain proteins 1 and 4 were tested and found to promote ADCC and

complement fixation.

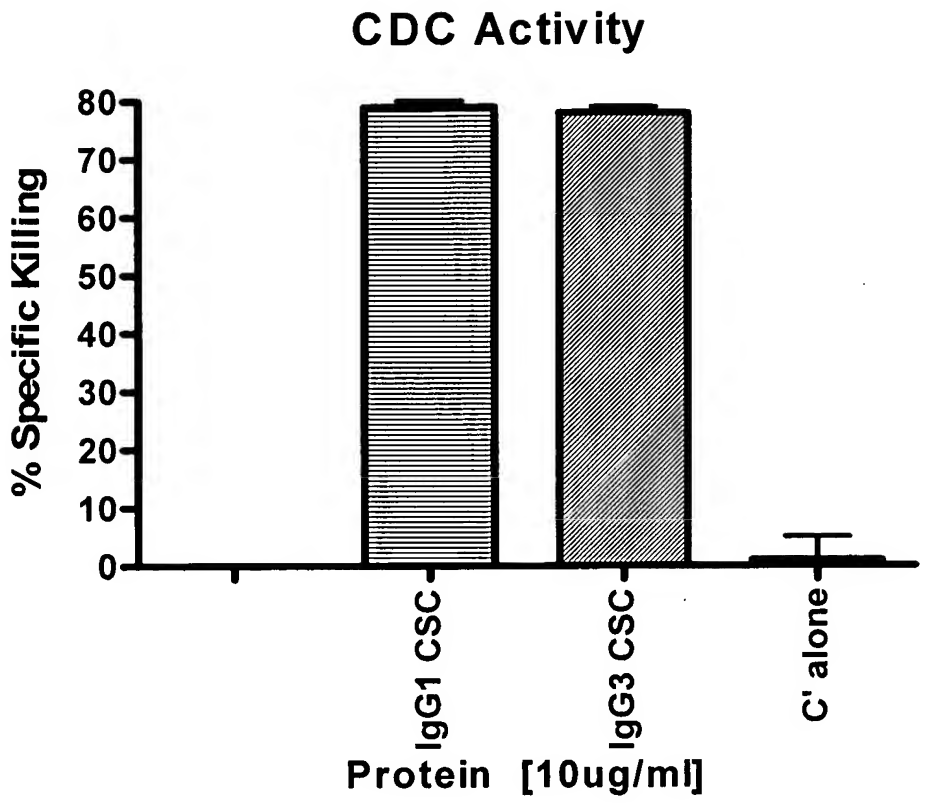
6. The ADCC assays were conducted as follows. Briefly, 1 x 10^7/ml BJAB B-cells were labeled with 500 uCi/ml ^{51}Cr sodium chromate (#CJS1, Amersham Biosciences, Piscataway, NJ) for 2 hrs at 37°C in Iscoves media (#12440-053, Gibco/Invitrogen, Grand Island, NY) with 10% FBS (#16140-071, Gibco/Invitrogen, Grand Island, NY). The 51Cr loaded BJAB were then washed 3 times in RPMI (#11875-093, Gibco/Invitrogen, Grand Island, NY) media with 10% FBS and resuspended at 4 x 10^5/ml in RPMI. Peripheral blood mononuclear cells (PBMC) from in-house donors were isolated from heparinized whole blood via centrifugation over Lymphocyte Separation Medium (#50494, MP Biomedicals, Aurora, OH), washed 2 times with RPMI media and resuspended at 5 x 10^6/ml in RPMI with 10% FBS. Single chain proteins were added to RPMI media with 10% FBS at 4 times the final concentration and three 10-fold serial dilutions for each single chain protein were prepared. These single chain proteins were then added to 96-well U- bottom plates at 50 ul/well for the indicated final concentrations. The ^{51}Cr labeled BJAB were then added to the plates at 50 ul/well (2 x 10^4/well). The PBMC were then added to the plates at 100 ul/well (5 x 10^5/well) for a final ratio of 25:1 effectors (PBMC):target (BJAB). Effectors and targets were added to media alone to measure background killing. The ^{51}Cr labeled BJAB were added to media alone to measure spontaneous release of ^{51}Cr and to media with 5% NP40 (#28324, Pierce, Rockford, IL) to measure maximal release of ^{51}Cr. The plates were incubated for 6 hours at 37°C in 5%CO_2 . Fifty ul (can use 25 ul) of the supernatant from each well were then transferred to a LumaPlate-96 (#6006633, Perkin Elmer, Boston, MA) and dried overnight at room temperature. In the morning, cpm were read on a Packard TopCount-NXT. Percent specific killing was calculated by subtracting cpm (mean of quadruplicant samples) of sample – cpm spontaneous release/cpm maximal release-cpm spontaneous release X 100. Figure 1 below shows the results of the assays.

Figure 1



7. The complement fixation assays were conducted as follows. In brief, approximately 3 x 10^5 Ramos B-cells were added per well to 96-well V-bottomed plates in 50 ul of Iscoves (#12440-053, Gibco/Invitrogen, Grand Island, NY) media (no FBS). The single chain proteins in Iscoves, (or Iscoves alone) were added to the wells in 50 ul at 2 times the indicated final concentration. The cells and single chain proteins were incubated for 45 minutes at 37°C. The cells were washed 2 ½ times in Iscoves with no FBS and resuspended in Iscoves with human serum (# A113, Quidel, San Diego, CA) in the 96-well plate at the indicated concentrations. The cells were then incubated for 90 minutes at 37°C. The cells were washed by centrifugation and resuspended in 125 ul cold PBS. The cells were transferred to FACs cluster tubes (#4410, CoStar, Corning, NY) and 125 ul PBS with propidium iodide (# P-16063, Molecular Probes, Eugene, OR) at 5 ug/ml was added. The cells were incubated with the propidium iodide for 15 minutes at room temperature in the dark and then placed on ice and read and analyzed on a FACsCalibur with CellQuest software (Becton Dickinson). The results of the assays are shown in Figure 2 below.

Figure 2



8. Single chain protein 1 (TRU-015) also exhibited a clinical benefit for rheumatoid arthritis patients in a Phase IIa study in humans. Results of the study were presented at the American College of Rheumatology Annual Scientific Meeting, Washington, DC during the week of November 10-15, 2006. A copy of the poster presented is attached as Exhibit 3. Furthermore, enrollment and dosing of patients has been completed for a Phase IIb clinical trial in human rheumatoid arthritis patients.

9. Other single chain proteins, described below, were made that include a binding domain capable of binding a target biological molecule joined to an IgG hinge peptide with one cysteine residue (the one cysteine being at the position responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG antibody) further joined to immunoglobulin heavy chain CH2 and CH3 constant region polypeptides.

Single chain protein	Binding domain target	Hinge	CH2	CH3
5	CD20	IgG_3 CSS	IgG_1	IgG_1
6	CD20	IgG_1 CSS	IgG_1	IgG_1
7	CD37	IgG_1 CSS	IgG_1	IgG_1

10. Like the two-cysteine single chain proteins, single chain protein 5 promoted ADCC and complement fixation activities when tested in the assays described above. See Figures 3 and 4.

Figure 3

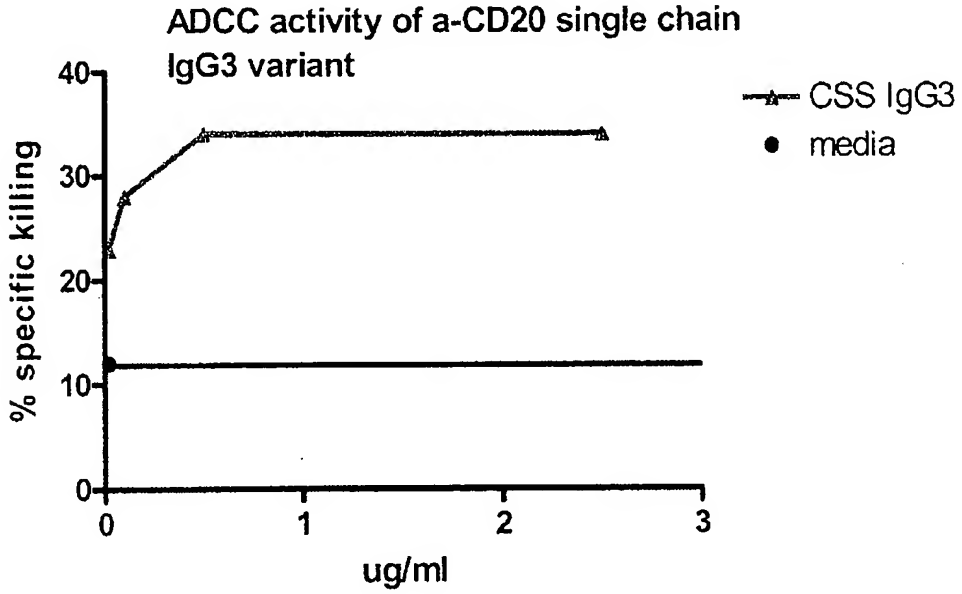
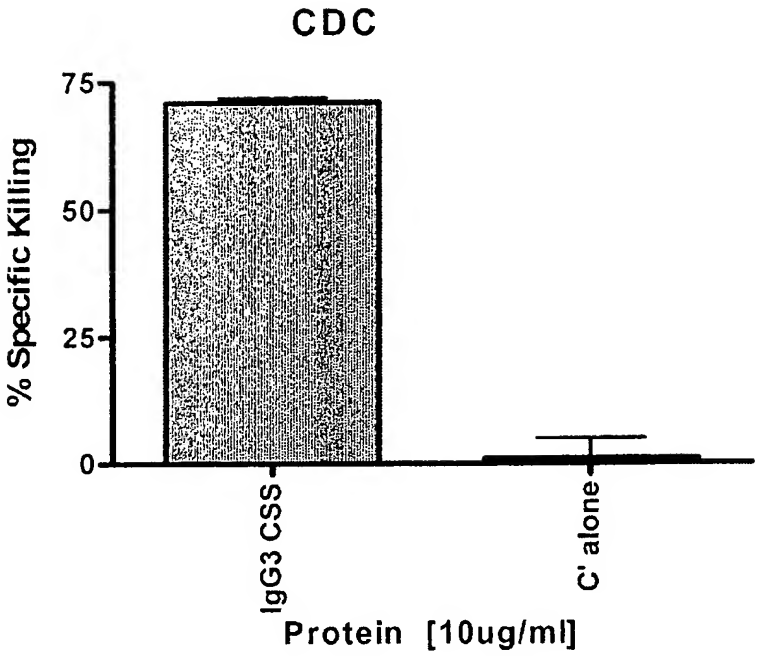


Figure 4



11. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

3/10/07
Date

Alan F. Wahl

Exhibit 1

CURRICULUM VITAE

NAME: Alan Francis Wahl

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Mercer Island WA, 98040
(206) 232-2783 (h)
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email: westwahl@comcast.net

INSTITUTION	DEGREE	YEAR
University of Rochester Rochester, NY	Ph.D. Biochemistry & Biophysics	1986
University of Rochester Rochester, NY	M.S. Biochemistry & Biophysics	1984
Rochester Institute of Technology, Rochester, NY	B.S. Biology/Chemistry *cum laude*	1978
Stanford University Stanford, CA	Postdoctoral Fellowship Experimental Oncology	1986-1989

PROFESSIONAL EXPERIENCE:

2006-present Vice President, Technology Research
Trubion Pharmaceutics, Inc. Seattle, WA 98121

Areas of Scientific Excellence:
- Discovery of novel biological immunotherapeutics for treatment of cancer and immunologic diseases.

Management Expertise:
- Member of Sr. management team responsible for corporate technical and strategic decisions.
- Scientific liaison for multiple strategic partners in Immunology and Oncology.
- Direct responsibility for Department of Technology Research of 14+ researchers

2000-2006 Senior Director, Molecular Oncology and Immunology
Seattle Genetics, Inc., Bothell, WA 98021

Areas of Scientific Excellence:
- Discovery and preclinical development of targeted biologics and small molecules for treatment of cancer and immunologic diseases.
- Identified and advanced numerous preclinical candidates
- Led preclinical IND teams for all Seattle Genetics' drugs currently in development or in clinical trials.
- Responsible for a strong in-house discovery/ development pipeline.

Management Expertise:
- Founding Director, Departments of Molecular Oncology and Immunology.
- Instrumental in building Seattle Genetics, Inc. from its 5-person inception to currently 140+ employees.
- Member of Senior Management Team reporting to CSO and Sr.VP.

- Chair, Late Stage Project Review Committee includes all aspects of drug discovery and experimental therapeutics.
- Key company representative for numerous in-licensing, out-licensing, investment and strategic alliances.
- Scientific liaison for multiple strategic partners in Immunology and Oncology.
- Direct responsibility for Departments of Molecular Oncology and Immunology and co-responsibility for Experimental Therapeutics Department. The former group includes an Associate Director and 12 researchers; the latter group includes 8 researchers.

1998-2000 Director, Biochemistry and Tumor Biology
Seattle Genetics, Inc., Bothell, WA 98021
Management Areas: Established company core competencies in Immunology, Tumor Cell Biology, and Experimental Therapeutics for drug discovery and development. Directly organized, staffed and grew departments of biology drug discovery and experimental therapeutics. Helped staff and shape Clinical, Development, Chemistry and Preclinical Development Departments for the newly formed company. Lead preclinical discovery and development teams, and successfully represented their accomplishments, including IND enabling studies to the company, investors and collaborators.

1997-1998 Principal Scientist
Department of Immunology
Zymogenetics Inc. Seattle WA 98102
Research Areas: Discovery and early stage development of biomolecules for treating immunologic diseases. Established immunologic / biochemical and tumor cell-based screens to detect signal transduction, proliferation and activation control of leukocytes and tumor cells.

1996-97 Principal Scientist and Group Leader
1992-1996 Senior Research Investigator II
Department of Inflammation, Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle WA, 98121
Research Areas: Mechanisms of apoptosis, proliferation and cell cycle control of leukocytes and neoplastic cells. Small molecule and biomolecule drug discovery for treatment of cancer and autoimmune diseases. Lead Scientist for development of proprietary cytokine clinical candidate for treatment of inflammatory diseases.
Management Areas: Responsible for evaluations and review of research of seven staff scientists and associates and for management review of external proposals to corporation. Participated in site visits for potential company or technology acquisitions. Direct reporting to V.P. Inflammation and Immunology. Responsible for departmental reporting to Bristol-Myers Squibb Corporate Drug Discovery Management Team.

1991-1992 Senior Research Investigator, Antitumor Cellular and Molecular Biology.
1989-1991 Research Investigator
Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT
Research Areas: Mechanism of anti-cancer drug action, platinol and taxane analog programs. Contributing scientist to TAXOL and Carboplatin programs. Enzymology of gene amplification and mechanisms of drug resistance in neoplasia.
Management Areas: Directed Core Facility for Synthetic Biomolecules, Bristol-Myers Squibb PRI, Wallingford, CT

POSTDOCTORAL RESEARCH FELLOWSHIP
1986-1989
Stanford University School of Medicine, Stanford, CA
Laboratory of Experimental Oncology, Department of Pathology
Advisors: Drs. T.S.-F. Wang and D. Korn

Research Area: Protein/DNA interactions during DNA replication in normal and neoplastic cell proliferation. Cloning, transcriptional regulation and cell cycle analysis of human DNA polymerase α.

GRADUATE RESEARCH
1981-1986

University of Rochester, Rochester, NY
Department of Biochemistry & Biophysics and The Cancer Center
Thesis Advisors: Drs. R.A. Bambara and E.M. Lord
Research Area: Purification, physicochemical characterization and enzymology of eukaryotic DNA dependent ATPases and replicative DNA polymerases. Cell fusion and monoclonal antibody production.
Thesis: *Mechanisms and Control of Mammalian DNA Replication.*

Awards: National Institutes of Health Molecular
Genetics Predoctoral Fellowship 1981-1985
Stanford University Deans Fellowship 1986-1987
National Cancer Institute Tumor Biology Training Fellowship 1987-1989

Society & Committee Memberships:
American Association for Cancer Research
American Association for the Advancement of Science
American Heart Association Review Committee 1994- 2000.
Member, Councils of Advisors, Gerson Lehrman Group, New York, NY
Ad hoc Reviewer for *Journal of Biological Chemistry, Biochemistry, Cancer Research, Clinical Cancer Research, Molecular and Cellular Biology, Blood, Bioconjugate Chemistry* and *Nature Medicine.*

STUDENT MENTORING:

Russell Sanderson	Ph.D. Postdoctoral Fellow	2003-2004
Andrew McShea	Ph.D. Postdoctoral Fellow	1996-1997
Mary Horne	Ph.D. Postdoctoral Fellow	1993-1995
Ellen Carmichael	Ph.D. Postdoctoral Fellow	1990-1992
Brian Spain	M.S. Stanford University	1987-1988

RESEARCH / RESEARCH MANAGEMENT SKILLS:

Molecular Biology: All stages of cDNA cloning and sequencing, PCR, Northern and Southern analysis, transcriptional regulation, analysis, and gene expression.

Cell Biology: Mammalian tissue culture, cell fusion, pathogenic microbiology, immunocytochemistry, in situ transcription, cell cycle separation and FACS analysis.

Tumor Biology: Tumor and primary cell culture, drug/drug interaction, growth control and apoptosis. Design, development and evaluation of in xenograft efficacy models of human carcinoma and hematologic neoplasia.

Inflammation: Design, development and evaluation of efficacy studies *in vitro* and animal models of arthritis, inflammatory bowel disease, pulmonary inflammation and multiple sclerosis.

Protein Chemistry:	Purification: HPLC, FPLC, RP, ion exchange, gel permeation and ligand affinity chromatography; chromato- and isoelectric focusing; synthesis of protein and nucleic acid based matrices, chromergenic and isotopic labeling.
Analysis:	Peptide sequencing, Amino Acid Analysis, PAGE, thin layer, 2-D peptide mapping, rate sedimentation and kinetics. ABI advanced peptide sequencer training.
Drug Development:	Authored preclinical sections to INDs for acytokine anti-inflammatory, a small molecule anti-cancer agent, and multiple antibody and antibody-drug conjugate anti-cancer clinical candidates. Authored numerous SOPs for drug development candidates.
Management:	Founded, developed and currently successfully manage two, highly productive departments within the organization. Organized and chaired committee for review and prioritization of late stage projects and represented these projects to corporate portfolio review committee.

PREDOCTORAL EMPLOYMENT

1979-1981	Senior Research Associate, Biochemistry Division, Eastman Kodak Research, Rochester, NY. Development of solid-state immunochemical assays. Purification of serum proteins, antigen/antibody production, biomolecule immobilization on synthetic supports.
1978	Research Technician, U.S. Centers for Disease Control, Albany, NY. Developed immunodiagnostics for Legionnaire's disease/Rocky mountain spotted fever. Rickettsia cell surface protein isolation and development of solid-phase immunoassays.
1976-1977	Area Administrator, National Technical Institute for the Deaf/R.I.T., Rochester NY. While a full time undergraduate student, directed a staff of 35 resident advisors to oversee a 2000-person residence complex for the hearing impaired.

TEACHING EXPERIENCE

1990	Adjunct Instructor, Department of Biological Sciences, Weslyan University, Middletown, CT. Instructed graduate course in Oncogenes and Growth Factors.
1982-1983	Teaching Assistant, Department of Biochemistry, University of Rochester Medical Center, Rochester NY. Graduate courses in Biochemistry and Advanced Biochemistry.
1976-1978	Instructor, National Technical Institute for the Deaf/ R.I.T. Co-developed curriculum and instructed leadership training and experiential education courses.

PUBLICATIONS

1. **A.F. Wahl**, J.W. Hockensmith, S.P. Kowalski and R.A. Bambara. (1983) Alternative explanation for excision repair deficiency caused by the polAexI mutation. J. Bacteriology, 155(2):982-986.

2. **A.F. Wahl**, S.P. Kowalski, L.W. Harwell, E.M. Lord, and R.A. Bambara. (1984) Immunoaffinity purification and properties of a high molecular weight calf thymus DNA-alpha polymerase. Biochemistry 23(9):1895-1899.

3. R.A. Bambara, J.J. Crute and **A.F. Wahl**. (1985) Is Ap4A an activator of eukaryotic DNA replication? Cancer Investigation. 3:473-479.

4. J.J. Crute, **A.F. Wahl**, R.A. Bambara. (1986) Purification and characterization of DNA polymerase delta from calf thymus. Biochemistry 25:26-36.

5. J.J. Crute, **A.F. Wahl**, R. Murant, R.A. Bambara, S.L. Gibson and R. Hilf. (1986) Inhibition of DNA polymerases in vitro and in vivo by hematoporphyrin derivative and photoradiation. Cancer Research. 46:153-159.

6. J.W. Hockensmith, **A.F. Wahl**, S. Kowalski and R.A. Bambara. (1986) Purification of calf thymus DNA-dependent ATPase that prefers a primer-template junction effector. Biochemistry 25:7812-7821.

7. **A.F. Wahl**, J.J. Crute, R.D. Sabatino, J.B. Bodner, R.L. Marraccino, L.W. Harwell, E.M. Lord and R.A. Bambara. (1986) Properties of two forms of DNA polymerase delta from calf thymus. Biochemistry 25: 7821-7827.

8. R.L. Marraccino, **A.F. Wahl**, P.C. Keng, E.M. Lord and R.A. Bambara. (1987) Cell cycle dependent activities of DNA polymerase alpha and delta in Chinese hamster ovary cells. Biochemistry 26:7864-7870.

9. S.W. Wong, **A.F. Wahl**, P.M. Yuan, N. Arai, B.E. Pearson, K. Arai, D. Korn, M. Hunkapiller and T.S.-F. Wang. (1988) Human DNA polymerase α gene expression is cell proliferation dependent and its primary structure is similar to both prokaryotic and eukaryotic replicative DNA polymerases. EMBO J. 7:37-47.

10. **A.F. Wahl**, A. Moore Geis, Brian H. Spain, W.W. Wong, D. Korn and T.S.-F. Wang. (1988) Gene expression of human DNA polymerase α during cell proliferation and the cell cycle. Molecular and Cellular Biology 8:5016-5025.

11. H.P. Nasheuer, A. Moore, **A.F. Wahl** and T.S.-F. Wang. (1991) Cell cycle-dependant phosphorylation of human DNA polymerase α. J. Biol. Chem. 266:7893-7903.

12. E.P. Carmichael, J. Roome and **A.F. Wahl**. (1993) Binding of a sequence-specific single stranded DNA binding factor to the SV40 core origin IR domain is cell cycle regulated. Molecular and Cellular Biology 13: 408-420.

13. L. Huang, J. J. Turchi, **A.F. Wahl** and R. A. Bambara. (1993) Effects of the anticancer drug *cis*-diamminedichloroplatinum (II) on the activities of calf thymus DNA polymerase ε. Biochemistry 32: 841-848.

14. L. Huang, J. J. Turchi, **A. F. Wahl** and R. A. Bambara. (1993) Activity of Calf Thymus DNA helicase ε on cis- diamminedichloroplatinum (II) damaged DNA. J. Biol. Chem. 268: 26731-26737.

15. K. Donaldson, G. Goolsby and **A. F. Wahl**. (1994) Cytotoxicity of the anticancer agents cisplatin and taxol during cell proliferation and the cell cycle. Int. J. Cancer 57: 847-855.

16. K. Donaldson, G. Goolsby, P. A. Kiener and **A. F. Wahl**. (1994) Activation of $p34^{cdc2}$ coincident with taxol-induced apoptosis. Cell Growth and Differentiation 5: 1041-1050.

17. G. L. Schieven, **A. F. Wahl**, S. Myrdal, L. Grosmaire and J. A. Ledbetter (1995) Lineage specific induction of B cell apoptosis and altered signal transduction by the phosphotyrosine phosphatase inhibitor Bis(maltolato) oxovanadium(IV). J. Biol. Chem. 270: 20824-20831.

18. P.A. Kiener, P. M. Davis, B. M. Rankin, **A. F. Wahl**, A. Aruffo and D. Hollenbaugh. (1995) Stimulation of CD40 with purified soluble gp39 induces proinflammatory responses in human monocytes. J. Immunol.155: 4917-4955.

19. **A. F. Wahl**, K. L. Donaldson, C. Fairchild, F. Y. F. Lee, S. A. Foster, G. W. Demers and D. A. Galloway. (1996) Normal p53 function confers resistance to Taxol by completion of mitosis and induction of G_1 arrest. Nature Medicine. 2:72-79.

20. M. C. Horne, G. L. Goolsby, K. L. Donaldson, D. Tran, M. Nuebauer and **A. F. Wahl** (1996) Cyclin G1 and G2 comprise a new family of cyclins with contrasting tissue specific and cell cycle regulated expression. J. Biol. Chem. 271:6050-6061.

21. N. Malik, B. W. Greenfield, **A. F. Wahl** and P. A. Kiener (1996) Activation of human monocytes through CD40 induces matrix metalloproteinases. J. Immunol. 156:3952-3960.

22. C.J. Barnes, **A. F. Wahl**, M. S. Park, B. Shen and R. A. Bambara (1996) Mechanism of tracking and cleavage of adduct damaged DNA substrates by the mammalian 5' to 3' exo/endonuclease RTH1/FEN1. J. Biol. Chem. 271:29624-29631.

23. K.L. Donaldson, A. ScShea and **A. F. Wahl** (1997) Separation by counterflow elutriation and analysis of T and B lymphocytes in progressive stages of the cell division cycle. J. Immunol. Meth. 203:25-33.

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25. A. McShea, P. L. Richey, K. W. Webster, **A. F. Wahl**, and M. A. Smith (1997) Cyclin-dependent kinase inhibitor p16 and Alzheimer's Disease: Evidence for reentry into the cell cycle. Am. J. Path. 150:1933-1939.

26. A. McShea, P. L. Harris, K.Webster, K., **A. F. Wahl**, and Smith, M.A. (1997) Abnormalities of cell cycle control elements in Alzheimer disease. Neurobiol. Aging, 18:683-.

27. P. M. Wallace, J. F. MacMaster, T. J. Brown, J. K. Loy, K. L. Donaldson, and **A. F. Wahl** (1999) Regulation of Inflammatory Responses by Oncostatin M. J. Immunol. 162:5547-55.

28. A. McShea, **A. F. Wahl**, and M. A. Smith (1999) Re-Entry into the cell cycle: A mechanism for neurodegeneration in Alzheimer's Disease. Med. Hypotheses. 52:525-527.

29. P. M. Wallace, J. F. MacMaster, T. J. Brown, J. K. Loy, K. L. Donaldson, and **A. F. Wahl** (1999) Regulation of Inflammatory Responses by Oncostatin M. J. Immunol. 162:5547-55.

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31. **A. F. Wahl** and K. L. Donaldson (1999) Separation of cells into progressive stages of the cell division cycle by counterflow centrifugal elutriation. Current Protocols in Cell Biology, Unit 8.6. (J. Wiley and Sons, New York, NY).

32. M. Jung, **A. F. Wahl**, W. Neupert, G. Geisslinger, and P. D. Senter (2000) Synthesis and activities of fluorinated derivatives of sulindac sulfide and sulindac sulfone. Pharm. Pharmacol. 6:217-221.

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34. **A. F. Wahl**, K. L. Donaldson, B. J. Mixan, P. A. Trail and C. B. Siegall (2001) Selective Tumor Sensitization to Taxanes with mAb-Drug Conjugate cBR96-Doxorubicin. International Journal of Cancer. 93:590-600.

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36. P. D. Senter, K. S. Beam, B. Mixan and **A. F. Wahl** (2001) Identification and activities of human carboxylesterases for the activation of CPT-11, a clinically approved anticancer drug. Bioconjugate Chemistry. 12: 1074-1080.

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38. **A. F. Wahl**, K. Klussman, J. Thompson, G. Risdon, D. Chace, C. B. Siegall and J. A. Francisco (2002) The anti-CD30 mAb SGN-30 induces apoptosis and affects antitumor activity in models of Hodgkin's Disease. Cancer Research, 62: 3736-3742.

39. S. O. Doronina, B. E. Toki, B. Mendelsohn, M. Torgov, C. G. Cerveny, D. F. Chace, S. Rejniak, R. DeBlanc, R. P. Gearing, C. B. Siegall, J. A. Francisco, **A. F. Wahl**, D. L. Myer, and D. D. Senter (2003), Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nature Biotechnology, 21: 778-794.

40. J. A. Francisco, C. G. Cerveny, D. L. Meyer, B. J. Mixan, K. Klussman, D. F. Chace, S. Rejniak, K. Gordon, R. DeBlanc, B. E. Toki, C.-L. Law, S. O. Doronina, C. B. Siegall, P. D. Senter and **A. F. Wahl** (2003) SGN-35, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood, 102: 1458-1465.

41. K. Klussman, B. Mixan, D. L. Meyer, P. D. Senter and **A. F. Wahl** (2004) Secondary mAb-vcMMAE conjugates are highly sensitive reporters of antibody internalization *via* the lysosome pathway. Bioconjugate Chemistry, 15:765-773.

42. J. Petroziello, A.Yamane, L. Westendorf, M. Thompson, C. McDonagh, C. Cerveny, C.-L, Law, **A. F. Wahl** and P. Carter, (2004) Suppression subtractive hybridization and expression profiling identifies a unique set of genes over-expressed in non-small cell lung cancer. Oncogene, 23:7734-7745.

43. C.-L.Law, C. G. Cerveny, K. Klussman, D. F. Chace, K. A. Gordon, D. L. Meyer, S. O. Doronina, C. B. Siegall, P. D. Senter, J. A. Francisco and **A. F. Wahl.** (2004). Efficient elimination of B-lineage lymphomas by anti-CD20 auristatin conjugates. Clinical Cancer Research, 10:7842-7851. *(Feature /Cover Article)*

44. R. J. Sanderson, M. A. Hering, S. F. James, M. M. C. Sun, S. O. Doronina, A. W. Siadak, P. D. Senter, and **A. F. Wahl**. (2005) *In vivo* drug linker stability of an anti-CD30 dipeptide-linked auristatin immunoconjugate. Clinical Cancer Research, 11:843-852.

45. C. G. Cerveny, C.-L. Law, R. S. McCormick, J. S. Lenox, K. J. Hamblett, L. E. Westendorf, A. K. Yamane, J.M. Petroziello, J. A. Francisco and **A. F. Wahl**. (2005) Signaling via the anti-CD30 mAb SGN-30 sensitizes Hodgkin's disease cells to conventional chemotherapeutics. Leukemia, 19:1648-1655.

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SGN-30. A chimeric monoclonal antibody for the treatment of hematologic malignancies. Seattle Genetics, Inc.
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Exhibit 2

TRU-015, A SMALL MODULAR IMMUNOPHARMACEUTICAL (SMIP™) DRUG CANDIDATE DIRECTED AGAINST CD20, DEMONSTRATES CLINICAL IMPROVEMENT IN SUBJECTS WITH RHEUMATOID ARTHRITIS

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Abstract

BACKGROUND: Protein therapeutics directed toward CD20-antigen on B lymphocytes have been demonstrated to be highly effective in the treatment of rheumatoid arthritis (RA).[1,2] SMIP™ drugs are single chain polypeptides that are smaller than antibodies. TRU-015 is a CD20-directed SMIP drug candidate that effectively depletes B lymphocytes in cynomolgus monkeys in a dose-dependent manner, and improves survival in mouse xenograft tumor models.[3,4]

OBJECTIVE: Previously, a dose escalation study in subjects with RA demonstrated that TRU-015 was generally well tolerated and resulted in dose dependent B lymphocyte depletion.[5] The present study was designed to further assess the safety and pharmacokinetics of TRU-015 and to additionally evaluate clinical responses in RA subjects with active disease treated with TRU-015.

METHODS: Thirty-seven RA subjects with active disease despite background methotrexate were enrolled in this randomized, double-blind, multi-center, placebo-controlled study. Subjects were enrolled into one of three cohorts in a 10:2 (active:placebo) ratio to receive TRU-015 as a single intravenous infusion of 5 mg/kg, two infusions of 2.5 mg/kg, or two infusions of 7.5 mg/kg. Subjects in cohorts with two infusions received the infusions one week apart. Subjects were generally pre-medicated with steroids without additional oral steroids.

RESULTS: Interim data is available in this ongoing study. TRU-015 was generally well tolerated. No significant infusion reactions were observed. No infectious or non-infectious SAEs related to TRU-015 have been reported. B cell depletion was demonstrated in all cohorts. The exposure of TRU-015 following two IV infusion of 2.5 mg/kg was comparable to that following a single infusion of 5 mg/kg. ACR 20 responses have been observed in 72% of all available subjects and 65% of RF+ subjects. At 12 weeks, response rates were similar in each of the cohorts. Longer-term observation is ongoing.

CONCLUSIONS: TRU-015, administered at doses resulting in B cell depletion, is generally well tolerated. No significant safety issues have been observed. This study provides evidence that therapy with TRU-015 results in meaningful clinical benefit in subjects with active RA despite methotrexate therapy. Further exploration is required to determine the optimal dose of TRU-015.

Background

Small Modular ImmunoPharmaceutical (SMIP) drugs

- SMIP drugs are single-chain polypeptides that are engineered for optimal potency in different diseases. These molecules are approximately one-third to one-half the size of conventional therapeutic monoclonal antibodies, yet they maintain in vivo half-life. SMIP drugs bind specifically to an antigen and have effector mechanisms designed into the molecule appropriate for the therapeutic indication.

CD20 and TRU-015

- CD20 directed therapy is well established in oncology, and was recently demonstrated to be highly effective in the treatment of rheumatoid arthritis.[1,2] SMIP drugs are smaller than antibodies yet are capable of utilizing effector functions of Fc mediated cellular cytotoxicity, complement mediated cytotoxicity and apoptotic signaling. TRU-015 is a SMIP drug candidate that is specific for CD20. TRU-015 has been demonstrated to effectively deplete B lymphocytes in cynomolgus monkeys in a dose-dependent manner, and improve survival in mouse xenograft tumor models.[3,4]

In a Phase 1 study, TRU-015 has been evaluated in subjects with rheumatoid arthritis.[5]

- TRU-015 was generally well tolerated and no dose limiting toxicity was observed.
- No neutralizing antibodies to TRU-015 have been observed.
- Infusions were generally well tolerated. As has been demonstrated with other protein therapeutics, corticosteroid pre-medication may be beneficial in preventing infusion related toxicities.
- TRU-015 therapy results in exposure to drug that is generally dose proportional. The serum half-life is similar to that seen with larger protein therapeutics.
- Treatment with TRU-015 resulted in dose dependent B cell depletion.

On the basis of these results, evaluation of subjects with active disease was warranted.

TRU-015 Phase 2a clinical study in subjects with rheumatoid arthritis

Objectives:

- To further assess the safety and tolerability of TRU-015 given by IV infusion in subjects with rheumatoid arthritis
- To evaluate the impact of different treatment regimens on the pharmacodynamics of TRU-015
- To provide proof of concept that B cell depletion with TRU-015 translates into meaningful clinical benefit.

Methods

Study Design

- Phase 2a multi-center, double-blind, randomized study to evaluate safety and pharmacodynamics of TRU-015 in subjects with rheumatoid arthritis. The study was also to establish proof-of-concept that B cell depletion with TRU-015 results in clinically meaningful responses.
- Inclusion/Exclusion Criteria:
  - Fulfill the 1987 ACR criteria for rheumatoid arthritis
  - Demonstrable active disease:
    - At least 6 tender and 6 swollen joints
    - At least one of the following:
      - Westergren ESR ≥ 28 mm/hr
      - C-reactive protein of at least 1.5 mg/dl
      - Morning stiffness of at least 45 minutes duration
  - Concomitant Medications:
    - Receiving stable dose of methotrexate (≤25 mg/week)
    - Receiving no other DMARDs or biologic agents
    - Receiving no more than 10 mg/day of prednisone or equivalent
  - Ages 18-70
  - Laboratory studies:
    - AST and ALT ≤ 2x upper limit of normal
    - Hemoglobin ≥ 8.5 gm/dL
    - Platelet count ≥ 125k/cmm³
    - WBC ≥ 3.0K cells/cmm³
    - Creatinine ≤ 2.0 mg/dL
  - No evidence of active or latent infection by exam or chest x-ray
  - No significant concurrent medical problems
- Each cohort contained 12 subjects; subjects were randomized in a 10:2 ratio to TRU-015 or placebo, cohorts were enrolled consecutively
- Subjects were pre-medicated with anti-histamine and acetaminophen. Most subjects received corticosteroid premedication.
- Based on results of the Phase 1 study, the following doses were selected for the Phase 2a study:
  - 5 mg/kg administered as a single infusion
  - 5 mg/kg administered as two infusions of 2.5 mg/kg (one week apart)
  - 15 mg/kg administered as two infusions of 7.5 mg/kg (one week apart)
- Subjects were followed for a minimum of 12 weeks. Those with B cell depletion were followed until recovery of B cells.
- Data from the first 24 weeks of observation are included in this analysis.
- TRU-015 serum concentration was measured at pre-determined timepoints
- Flow cytometric evaluation of peripheral blood was performed at each visit; CD19 was used to measure the number of B cells

Results

Demographics (N=31)

Gender:	Female 77%; Male 23%
Ethnicity:	84% Caucasian (non-Hispanic); 13% Hispanic; 3% African American
Mean age (range 31-73):	56
Mean weight:	78 kg
Mean duration of disease (range):	6.9 years (0-35)

Discontinuations

- 2 subjects discontinued from study prior to 24 weeks
  - one subject was lost to follow up after the 12 week evaluation; one subject withdrew consent in the 14th week

Safety

Adverse Event	N	%
Headache	14	45.2
Upper Resp Infect	6	19.4
Bronchitis	5	16.1
Fatigue	5	16.1
Pruritus	5	16.1
Urinary Tract Infection	4	12.9
Insomnia	4	12.9
Nausea (1 episode quarter)	4	12.9

Adverse event rates in the placebo and active subjects were not significantly different for any adverse event in this proof-of-concept study.

Serious Adverse Events

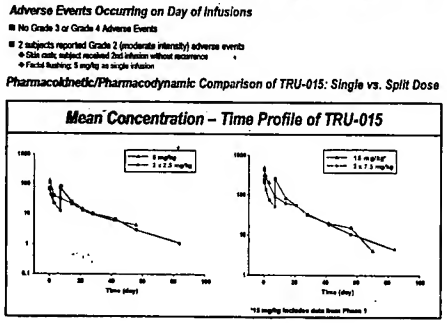
- One serious adverse event was reported during the 24 week period. A 40 yo white female developed cholecystitis 5 months after study drug administration. The subject underwent cholecystectomy without complication.

Adverse Events Occurring on Day of Infusions

- No Grade 3 or Grade 4 Adverse Events
- 2 subjects reported Grade 2 (moderate intensity) adverse events
  - Skin rash; subject received 2nd infusion without recurrence
  - Facial flushing; 5 mg/kg as single infusion

Pharmacokinetic/Pharmacodynamic Comparison of TRU-015: Single vs. Split Dose

Mean Concentration – Time Profile of TRU-015



*15 mg/kg includes data from Phase 1

TRU-015 PK Parameters

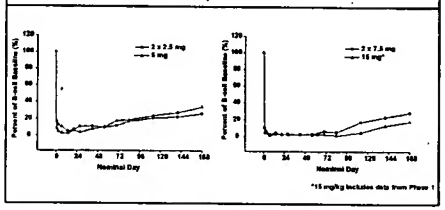
Treatment	C_{max} (ng/mL) mean	C_{max} (ng/mL) CV%	AUC_{inf} (ug*hr/mL) mean	AUC_{inf} (ug*hr/mL) CV%
2 x 2.5 mg	89.9	21.9	24678	25.4
5 mg	135	14.2	23704	81.1
2 x 7.5 mg	297	24.1	70383	27
15 mg	550	9.5	86934	26.6

At a total dose of either 5 mg/kg or 15 mg/kg, AUC exposures of TRU-015 given as a single IV infusion were similar to that of two IV infusions of equally divided doses separated by 1 week.

Pharmacodynamics

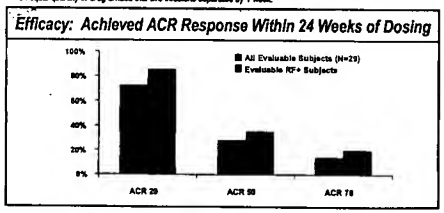
- B cells were evaluated by measuring CD19+ cells at screening, baseline, and post-infusion on days 1, 3, 7, 14, 21, 28, and then every 2-4 weeks thereafter until recovery of B cells.

B-cell Depletion Profile



- At a total dose of TRU-015 of 5 mg/kg and 15 mg/kg, a single infusion resulted in a similar duration of B- cell depletion as an equal quantity of drug divided into two infusions separated by 1 week.

Efficacy: Achieved ACR Response Within 24 Weeks of Dosing



Immunogenicity

All subjects were evaluated for the presence of neutralizing antibodies to TRU-015. To date, no serum samples have tested positive for neutralizing antibodies. Patients with TRU-015 present in the serum at the time of the assay require further evaluation for antibodies when TRU-015 is no longer present.

Conclusions

- TRU-015 administered to subjects with rheumatoid arthritis is generally well tolerated. Adverse events to date have been mostly mild to moderate.
- Infusions have been generally well tolerated.
- Pharmacokinetic and pharmacodynamic measures indicate that a single dose is likely to provide similar benefit when compared to the same quantity of drug administered in divided doses.
- No neutralizing antibodies to TRU-015 have been detected to date.
- B Cell depletion occurring with TRU-015 therapy is associated with meaningful clinical responses.
- A dose-ranging study of TRU-015 in subjects with active rheumatoid arthritis is warranted to optimize the dose and schedule of TRU-015

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